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Secondary Failure of Platelet Recovery After Hematopoietic Stem Cell Transplantation

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ABSTRACT

After primary recovery of platelet counts after transplantation, there can be a late persistent decline called secondary failure of platelet recovery (SFPR), which may occur although the counts of other cell lineages remain within the normal range. SFPR was defined as a decline of platelet counts below 20,000/μL for 7 consecutive days or requiring transfusion support after achieving sustained platelet counts ≥50,000/μL without transfusions for 7 consecutive days after hematopoietic stem cell transplantation (HSCT). The study population consisted of 2871 consecutive patients receiving transplants from January 1990 to March 1997. After primary recovery of platelet counts, SFPR not due to relapse of the underlying disease was observed in 285 of 1401 (20%) patients undergoing allogeneic transplantation and 36 (8%) of 444 patients undergoing autologous transplantation, with a median time of onset after transplantation at day 63 (range, day 21-156) and day 44 (range, day 24-89), respectively. Concomitant neutropenia was seen in 57 (20%) of 285 patients undergoing allogeneic HSCT and 7 (19%) of 36 patients undergoing autologous HSCT with SFPR. By multivariable analysis, the following were factors significantly associated with SFPR after allogeneic HSCT: a transplant from an unrelated donor; a graft-versus-host disease (GVHD) prophylaxis other than methotrexate and cyclosporine; development of grade 2 through 4 acute GVHD; impaired renal or liver function; conditioning with the combination of busulfan, cyclophosphamide, and total body irradiation; stem cell dose; and infections. Cytomegalovirus infection after engraftment and source of stem cells were the only significant risk factors after autologous HSCT. The hazard rate of death was significantly higher in patients who experienced SFPR (hazard ratio = 2.6 for allogeneic HSCT; hazard ratio = 2.2 for autologous HSCT). SFPR was associated with serious complications and poor outcome after transplantation. The identification of the characteristics and risk factors for SFPR could improve patient counseling and management and lead to the design of effective treatment strategies.

KEY WORDS

Bone marrow transplantation • Platelets • Graft-versus-host disease • Leukemia • Thrombocytopenia

INTRODUCTION

Severe thrombocytopenia is the inevitable consequence of myeloablative conditioning regimens used for hematopoietic stem cell transplantation (HSCT). Severe thrombocytopenia necessitates platelet transfusion for the management and prevention of bleeding. The speed of recovery of platelet counts after both autologous and allogeneic HSCT is dependent on several factors, including source of stem cells, cell doses infused, types and phases of disease, graft-versus-host disease (GVHD), infections, and cytomegalovirus (CMV) serology at transplantation [1-8].

After primary recovery of peripheral blood counts after transplantation, there can be a late decline of platelet counts, although the counts of other cell lineages may remain near or in normal ranges. This secondary failure of platelet recovery (SFPR) can result in prolonged severe

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thrombocytopenia in which patients again require platelet support. Thrombocytopenia can result from different factors that either affect the production of platelets in the marrow or cause decreased platelet survival in the peripheral circulation. Disease recurrence and allograft rejection are important causes of thrombocytopenia. Nonetheless, transplant patients can develop isolated thrombocytopenia in the absence of disease relapse or graft rejection, indicating the existence of other pathophysiological mechanisms that are currently poorly defined. This study describes the incidence, clinical features, risk factors, and outcome of SFPR due to causes not related to disease recurrence in a large series of patients undergoing HSCT.

MATERIALS AND METHODS

Study Population

The study population consisted of 2871 consecutive patients undergoing HSCT at the Fred Hutchinson Cancer Research Center (FHCRC) between January 1, 1990, and March 31, 1997. All patients were treated after obtaining informed consent. Data for long-term follow-up was collected on FHCRC Protocol 999. Clinical and laboratory data were extracted from the computerized database and from the research charts. Patients were categorized according to type of transplant (allogeneic versus autologous). All patients were evaluated from the day of transplantation, defined as day 0, until the first occurrence of one of the following events: relapse, second transplantation, last routine follow-up before discharge to home, or death.

Definitions

Primary platelet recovery after myeloablative conditioning regimens was defined as an increase in platelet counts to ≥50,000/μL for 7 consecutive days without transfusion support. SFPR was defined as a decline of platelet counts below 20,000/μL, lasting at least 7 consecutive days or requiring platelet transfusions within 7 days, after achieving primary platelet recovery. The first of the 7 consecutive days of thrombocytopenia with platelet counts below 20,000/μL was considered the day of onset of SFPR.

Risk Factor Analysis

To identify risk factors associated with the hazard rate of development of SFPR, the following variables were evaluated: age at transplantation, patient sex, type of donor, source of stem cells (bone marrow versus peripheral blood), cell dose infused (either $CD34^+$ cell or total nucleated cell counts), conditioning regimens, CMV serology at transplantation, pretransplantation platelet count, and presence of underlying disease. These underlying diseases were further categorized as low risk, intermediate risk, and high risk. The low-risk group was composed of patients with chronic myelogenous leukemia (CML) in the chronic phase. The high-risk group was composed of patients in relapse undergoing transplantation and CML patients in blast crisis. All other patients were categorized into the intermediate-risk group. For patients undergoing allogeneic HSCT, other variables included in the analysis were patient/donor sex, patient/donor CMV status at transplantation, development of acute GVHD, and GVHD prophylaxis other than methotrexate (MTX) plus cyclosporine (CSP)—the current standard regimen at our institution [9].

Renal and liver functions were evaluated based on serum creatinine and bilirubin levels, respectively, and were considered continuous variables throughout the study period. Infections were evaluated from the time of primary platelet recovery in all patients. Systemic bacterial and fungal infections were documented by positive blood cultures. Viral infections were documented by the onset of viremia or by positive centrifugation cultures (shell vial) from blood samples and/or detection of positive antigenemia for CMV.

In patients who developed SFPR, the incidence of concomitant neutropenia was assessed, defined as at least 2 consecutive absolute neutrophil counts (ANC) of <1000/μL on 2 different days during the week before or after the day of onset of SFPR. Presence of the thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS) was based on chart review of haptoglobin, lactate dehydrogenase (LDH), and serum creatinine values; Coombs test; the presence of schistocytes on the peripheral blood smear; and the documented evaluations of primary care providers and attending physicians. LDH was considered abnormally high if it was >250 U/dL, whereas haptoglobin was considered abnormally low if it was <26 mg/dL. The criteria for the diagnosis of TTP/HUS were the presence of Coombs-negative hemolytic anemia with schistocytes and thrombocytopenia with or without renal abnormalities.

Marrow Assessment

Pathology reports of bone marrow aspirates, obtained from the posterior iliac crest of thrombocytopenic patients after the onset of SFPR and adjusted for age categories [10], were reviewed to correlate marrow cellularity and presence of megakaryocytes with SFPR. Data on cellularity were divided into 3 groups: marrow cellularity with and without the presence of megakaryocytes <35% of normal, ≥35% but <50% of normal, and ≥50% of normal.

Transfusion Requirements

The platelet transfusion guidelines at our center before 1993 were to maintain platelet counts above 20,000/μL. After 1993, stable patients followed as outpatients received transfusions at platelet counts <10,000/μL, whereas inpatients, if less stable or early after HSCT, routinely received transfusions at platelet counts <20,000/μL. For invasive diagnostic procedures required after HSCT, it was standard practice to maintain platelet counts of >20,000/μL for 1 day for bronchoscopy, ≥50,000/μL for 1 day for central line placement or lumbar punctures, ≥50,000/μL for 3 days for endoscopy of the gastrointestinal tract with biopsy, and >50,000 to 70,000/μL for 5 days for major surgery.

In the present article, platelet transfusion requirements were determined for all patients from transplantation to the day of second transplantation, discharge home, relapse, or death. Total transfusion events, in addition to total transfusion events divided by the number of days of observation, were assessed. A single transfusion event was considered equivalent to a pool of 6 units of random-donor platelets obtained from whole-blood units or single-donor platelets collected by platelet pheresis. A more formal comparison of transfusion requirements among the groups listed was not

Table 1. *Patient Characteristics**

	Allogeneic Patients	Autologous Patients
n	1401	444
Age at transplantation, y	34.8 (0.3-67.0)	43.6 (0.4-68.3)
Cell dose, TNCs $\times 10^6$ per kg	2.6 (0.05-36.3)	6.2 (0.1-80.0)
Patient/donor sex		
M/M	449 (32)	168 M (38)
M/F	317 (23)	—
F/M	364 (26)	276 F (62)
F/F	271 (19)	—
Median baseline platelet count	76,000	112,000
Acute GVHD		
Grades 0-1	393 (28)	—
Grades 2-4	967 (69)	—
Unknown	41 (3)	—
Type of donor		
Matched sibling	758 (54)	—
Mismatched related	190 (14)	—
Unrelated	450 (32)	—
Source of stem cells		
Bone marrow	1296 (93)	137 (31)
Peripheral blood	101 (7)	286 (64)
Bone marrow and peripheral blood	4 (<1)	21 (5)
Diagnosis		
Low-risk	423 (30)	7 (2)
Intermediate-risk	561 (40)	172 (23)
High-risk	417 (30)	265 (39)
Conditioning regimen		
TBI >12 cGy	581 (41)	4 (1)
TBI ≤12 cGy	304 (22)	104 (23)
BuCy	326 (23)	61 (14)
BuCy TBI	80 (6)	39 (9)
Other	110 (8)	236 (53)
GVHD prophylaxis		
MTX + CSP	1267 (90)	—
Other	134 (10)	—

*Data are median (range) or n (%). TNC indicates total nucleated cell; GVHD, graft-versus-host disease; TBI, total body irradiation; Bu, busulfan; Cy, cyclophosphamide; MTX, methotrexate; CSP, cyclosporine.

done because the transfusion requirements contributed to the definition of each group.

Long-Term Follow-Up

Data on 1-year mortality, causes of death, and late complications were obtained from research charts, hometown physician notes, and autopsy reports. Platelet recovery from SFPR was assessed in patients alive at 1 year and defined as recovery of self-sustained platelet counts of >50,000/μL, as described above, that occurred within 1 year ± 3 months from transplantation. This time frame was chosen to evaluate all data collected from primary physicians or obtained from the work-up performed for the 1-year follow-up evaluation at the FHCRC.

Statistical Methods

Proportional hazard rate regression models were fit to examine the association of the factors previously listed with the of SFPR among patients who achieved primary platelet recovery. The data were left truncated so that a patient did not enter the risk set for SFPR until primary platelet recovery was achieved. Patients who were classified as not having failed were censored in regression models at the minimum of time of death, second transplantation, discharge home, or relapse. Patients who relapsed within 30 days from the onset of SFPR were reclassified as not having failed. Interactions between selected variables were examined as needed in regression models, and the assumption of proportional hazard rates was tested by including a term representing the logarithm of time (where time represents time to SFPR). The effect of SFPR on mortality was examined among patients who achieved primary platelet recovery using proportional hazard rates regression models. SFPR was regarded as a time-dependent covariate for these purposes, and the data were left truncated as before. Patients, therefore, were not regarded as failures until the time of SFPR, and patients did not enter the risk set until primary recovery was achieved. Treating SFPR as a time-dependent covariate dealt with the lead-time bias that was incurred by categorizing patients as failures posttransplantation. Explanatory variables that were correlated were examined by comparing regression models with both sets of variables to models containing only 1 set of the correlated variables using the likelihood ratio test. All analyses were conducted separately for the data from autologous and allogeneic transplants. All *P* values associated with regression models were derived from the Wald test, and no adjustments were made for multiple comparisons.

RESULTS

Secondary Failure of Platelet Recovery After Allogeneic Stem Cell Transplantation

A total of 2153 patients received an allogeneic transplant during the study period, and 1401 (65%) achieved primary platelet recovery. After primary platelet recovery, 821 of 1401 (59%) maintained platelet counts of ≥50,000/μL for the entire observation period. Of the 1401 patients, 250 (18%) had a decline to <50,000/μL but not <20,000/μL after primary recovery, and the remaining 330 (24%) had a decline to <20,000/μL after primary recovery. Of the 330 patients, 45 relapsed within 1 month of SFPR and were regarded as nonfailures for the purposes of the analysis. Characteristics of patients who achieved primary recovery are reported in Table 1.

The adjusted incidence of SFPR not due to disease recurrence was 20% (285/1401). Median day of onset was day 63 (range, day 21-156) posttransplantation. Of the 70% (199/285) of patients who were discharged home at a median of day 103 (range, day 61-305), only 28% (56/199) had recovered to sustained platelet counts >50,000/μL by the time of discharge, with a median duration of SFPR of 25.5 days (range, day 3-89). The overwhelming majority (96.2%) of patients who did not develop SFPR had follow-up discontinued because they were discharged home. The median duration of the observation period of these patients was 94 days.

Overall, 141 patients who developed SFPR were alive at 1 year. At this time, 86% (121/141) had platelet counts >50,000/μL (64% [77/121] had platelet counts >150,000/μL), and 6% (8/141) had platelet counts <50,000/μL. Data on platelet counts were available on the other 11 patients

Table 2. *Univariate Models for Secondary Failure of Platelet Recovery Among Allogeneic and Autologous Patients**

	Hazard Ratio	95% CI	P
Allogeneic patients			
Age at transplantation†	1.1	1.0-1.2	.007
Disease risk			
Low	1	—	—
Intermediate	1.2	0.9-1.6	.25
High	1.4	1.1-1.9	.02
Preparative regimen			
TBI ≤12 cGy	1	—	—
TBI >12 cGy	1.2	0.9-1.6	.21
BuCy	0.6	0.4-0.9	.009
BuCy TBI	1.7	1.1-2.7	.02
Other	1.0	0.6-1.6	.89
Patient/donor CMV serology			
–/–	1	—	—
–/+	0.8	0.5-1.2	.30
+/–	0.8	0.6-1.2	.27
+/+	1.1	0.8-1.5	.46
Patient sex			
M	1	—	—
F	1.0	0.8-1.3	.78
Patient/donor sex			
M/M	1	—	—
M/F	1.0	0.7-1.4	.96
F/M	1.1	0.8-1.5	.38
F/F	0.9	0.6-1.3	.51
Type of donor			
Matched sibling	1	—	—
Related HLA-mismatched	1.2	0.9-1.8	.22
Unrelated	1.5	1.1-1.9	.003
GVHD prophylaxis			
Other regimen	1	—	—
CSP + MTX	0.5	0.4-0.8	.0007
Acute GVHD‡			
Grades 0-1	1	—	—
Grades 2-4	4.7	3.2-7.1	<.0001
Cell dose§	0.98	0.94-1.02	.31
Baseline platelet count‖	0.94	0.89-0.99	.02
Bilirubin level¶	1.2	1.1-1.2	<.0001
Creatinine level¶	1.6	1.2-2.1	.0004
Infections‡			
Bacterial	2.3	1.8-2.9	<.0001
Fungal	6.2	3.8-10.0	<.0001
CMV	1.6	1.2-2.1	.0004
Autologous patients			
Age at transplantation†	1.3	1.0-1.7	.08
Disease risk			
Intermediate	1	—	—
Low	0.4	0.1-1.2	.09
High	0.7	0.3-1.6	.38
Preparative regimen			
TBI ≤12 cGy	1	—	—
TBI >12 cGy	—	—	—
BuCy	0.4	0.1-1.9	.24
BuCy TBI	2.1	0.8-5.9	.14
Other	1.1	0.5-2.5	.83
Patient CMV serology			
Negative	1	—	—
Positive	1.7	0.8-3.6	.17
Patient sex			
M	1	—	—
F	1.1	0.6-2.2	.80
Source of stem cells			
BM	1	—	—
PBSCs	2.4	1.0-5.7	.05
BM + PBSCs	4.8	1.5-15.1	.008
Cell dose§	1.02	1.0-1.04	.07
Baseline platelet count‖	0.90	0.70-1.15	.39
Bilirubin level¶	1.1	0.9-1.3	.34
Creatinine level¶	1.3	0.4-4.5	.71
Infections‡			
Bacterial	1.3	0.5-3.3	.62
Fungal	2.8	0.7-11.5	.16
CMV	4.4	1.9-10.1	.0004

*TBI indicates total body irradiation; Bu, busulfan; Cy, cyclophosphamide; CMV, cytomegalovirus; GVHD, graft-versus-host disease; CSP, cyclosporine; MTX, methotrexate; BM, bone marrow; PBSC, peripheral blood stem cell.

†Modeled as a continuous variable; hazard ratio is presented per decade.

‡Treated as a time-dependent covariate.

§Modeled as a continuous variable; hazard ratio presented per 1×10^6 cells/kg.

‖Modeled as a continuous variable; hazard ratio presented per 50,000 platelets/μL.

¶Treated as a time-dependent covariate, where the covariate is the average value of the appropriate parameter in a 15-day interval. Treated as a continuous variable; 1 U = 1 mg/dL.

between 4 and 9 months (n = 2) or after 15 months (n = 9), all of whom had platelet counts >50,000/μL. There was 1 patient for whom there was no long-term data on platelet counts. Clinical extensive chronic GVHD occurred in 71% (101/141) of these patients, and 2.5% (5/141) of patients had limited chronic GVHD.

Concomitant neutropenia was seen in 20% (57/285) of patients, and of these, 56% (32/57) were on ganciclovir. Thrombocytopenia was ascribed to TTP/HUS in 5% (15 of 285) of patients. Bacterial and fungal infections were documented in 24.5% (70 of 285) of patients after primary platelet engraftment. CMV infection was documented in 27% (79 of 285) of patients by CMV antigenemia (24% [69 of 285]) or by blood culture (11.5% [33 of 285]). No cases of graft rejection were identified in this group of patients with SFPR.

Bone marrow aspirates were performed in 64% (183 of 285) of thrombocytopenic patients at a median of 11 days (range, 0-72 days) after the onset of SFPR. Overall cellularity was read as <35% of normal in 35% (64 of 183) of patients, with 61 of the 64 (95%) showing trilineage engraftment and 3 (5%) showing amegakaryocytosis. Cellularity was ≥35% but <50% of normal in 14% (25 of 183) of patients, with 1 of the 25 (4%) showing relative reduction of megakaryocytes. Cellularity with trilineage engraftment was read as ≥50% of normal in 51% (94 of 183) of patients, with relative reduction of megakaryocytes in 6% (6 of 94).

Risk Factor Analysis. Univariate models for SFPR are illustrated in Table 2. By multivariable analysis, transplants from unrelated donors, GVHD prophylaxis other than

Table 3. *Risk Factors Associated With the Development of Secondary Failure of Platelet Recovery by Multivariable Regression**

	Hazard Ratio	95% CI	P
Allogeneic patients			
Type of donor			
Matched sibling	1.0	—	—
Related HLA-mismatched	1.2	0.8-1.8	.41
Unrelated	1.4	1.0-2.0	.03
GVHD prophylaxis			
Other regimen	1.0	—	—
CSP + MTX	0.5	0.3-0.7	.0006
Acute GVHD			
Grade 0-1	1.0	—	—
Grade 2-4	3.5	2.2-5.5	<.0001
Preparative regimen			
TBI ≤12 cGy	1	—	—
TBI >12 cGy	1.3	0.9-1.8	.14
BuCy	0.9	0.6-1.4	.59
BuCy TBI	2.0	1.1-3.4	.02
Other	1.8	1.0-3.2	.05
Average bilirubin level†‡ (as continuous variable)	1.13	1.09-1.17	<.0001
Average creatinine level†‡ (as continuous variable)	1.9	1.4-2.5	<.0001
Infections†			
Bacterial	1.8	1.3-2.3	<.0001
Fungal	4.1	2.4-7.1	<.0001
CMV	1.4	1.1-1.9	.01
Autologous patients			
Infections†			
CMV	4.0	1.7-9.1	.001
Source of stem cells			
BM	1	—	—
PBSCs	2.1	0.9-5.0	.10
BM + PBSCs	4.5	1.4-14.5	.01

*GVHD indicates graft-versus-host disease; CSP, cyclosporine; MTX, methotrexate; TBI, total body irradiation; Bu, busulfan; Cy, cyclophosphamide; CMV, cytomegalovirus; BM, bone marrow; PBSC, peripheral blood stem cell.

†Modeled as a time-dependent covariate (for bilirubin and creatinine levels, 1 U = 1 mg/dL).

‡Value taken as average level in 15-day windows.

MTX plus CSP, stem cell dose per kilogram, and preparative regimen were variables significantly associated with the hazard rate of SFPR among patients achieving primary recovery (Table 3). Development of acute GVHD, impaired renal and liver functions, and infections after primary platelet recovery were time-dependent variables significantly associated with the hazard rate of SFPR. After consideration of each of these variables, none of the other factors examined significantly improved the model (as determined by the likelihood ratio test). Prophylaxis for GVHD and preparative regimen were each associated with the risk of the underlying disease. A higher proportion of high-risk patients for the underlying disease received prophylaxis other than MTX and CSP, and patients who received >12 cGy total body irradiation (TBI) or the combination of busulfan, cyclophosphamide, and TBI were more likely to be high- or intermediate-risk patients. Type of donor and GVHD prophylaxis were also correlated with the development of acute GVHD. If underlying disease risk was added to the model summarized in Table 3, the resulting model was not significantly improved ($P = .85$). If, on the other hand, underlying disease risk was substituted for GVHD prophylaxis in the model shown in Table 3, addition of prophylaxis to such a model provides a significant improvement ($P = .004$). If preparative regimen is deleted from the model shown in Table 3, adding this variable suggestively improves the model ($P = .02$). If underlying disease risk replaces preparative regimen in Table 3, addition of preparative regimen to the resulting model yields a suggestive improvement ($P = .07$). If GVHD prophylaxis, occurrence of GVHD grades 2 through 4, or donor type is deleted from the model in Table 3, addition of each of these variables significantly or suggestively improves the model resulting from the deletion of each variable ($P = .003$, $P < .0001$, $P = .10$, respectively).

Platelet Transfusion Requirements. Transfusion requirements for patients who received allogeneic transplants are reported in Table 4. The patients with SFPR required more transfusion support.

Survival. The 1-year mortality of the patients developing SFPR was 51% (144/285). Of the patients, 30% (86/285) died before leaving FHCRC, and 21% (58/285) died after being discharged home. Causes of death are reported in Table 5. No graft rejection events occurred as a cause of death. When treated as a time-dependent covariate, development of SFPR was significantly associated with an increased hazard rate of mortality (hazard ratio = 2.6; 95% CI, 2.1-3.1, $P < .0001$) among patients who achieved primary recovery after adjusting for patient age at transplantation, risk of disease, GVHD prophylaxis, patient/donor CMV serostatus, type of donor, and preparative regimen. A total of 86% (48/56) of patients who had platelet recovery

Table 4. *Platelet Transfusion Requirement**

	Transfusion Events	Transfusion Events/ Days at Risk
Allogeneic patients		
>50,000/μL	8 (0-78)	0.08 (0-1.4)
20,000-50,000/μL	11.5 (2-95)	0.11 (0.02-1.22)
SFPR (<20,000 μL)	22 (4-167)	0.23 (0.03-1.37)
Autologous patients		
>50,000/μL	5 (0-85)	0.09 (0-0.89)
20,000-50,000/μL	6 (0-85)	0.1 (0-0.9)
SFPR (<20,000/μL)	13 (1-133)	0.15 (0.01-0.15)

*Data are median (range). SFPR indicates secondary failure of platelet recovery. All patients achieved primary platelet recovery and maintained platelet counts >50,000/μL, decreased to 20,000 to 50,000/μL, or had SFPR (<20,000/μL). Transfusion Events refers to the median total number of transfusion events (a single transfusion event was considered the equivalent to a pool of 6 U of random-donor platelets obtained from whole-blood units or single-donor platelets collected by platelet pheresis) administered per patient throughout the study period. Transfusion Events/Days at Risk refers to the median number of transfusion events administered per patient per day during the observation period.

Table 5. *Causes of Death at the 1-Year Follow-Up of Patients Developing Secondary Failure of Platelet Recovery**

	Allogeneic Patients	Autologous Patients
Total number	**144**	**16**
Other infections/sepsis	**46 (31)**	**2 (12.5)**
Graft-versus-host disease	**27 (18)**	**—**
Noninfectious pulmonary complications	**26 (18)**	**3 (19)**
Aspergillus pneumonia	**25 (17)**	**—**
Cytomegalovirus pneumonia	**15 (10)**	**—**
Venous occlusive disease	**11 (8)**	**5 (31)**
Hemorrhage	**11 (8)**	**1 (6)**
Relapse†	**10 (7)**	**2 (12.5)**
TTP/HUS	**2 (1.5)**	**1 (6)**
Other	**—**	**4 (25)**

*Data are n or n (%). TTP/HUS indicates thrombotic thrombocytopenic purpura/hemolytic uremic syndrome.

†Relapse occurred >1 month after the onset of secondary failure of platelet recovery.

by the time of discharge home and 65% (93/143) who were still thrombocytopenic upon discharge were alive at 1 year.

Secondary Failure of Platelet Recovery After Autologous Stem Cell Transplantation

A total of 718 patients received an autologous transplant during the study period, and 444 (62%) achieved primary platelet recovery. After primary platelet recovery, 353 (80%) of 444 patients maintained platelet counts ≥50,000/μL for the entire observation period. Of the 444 (11%) patients, 51 had a decline in platelet count to <50,000/μL but not <20,000/μL after primary recovery, and the remaining 40 (9%) had a decline in platelet count to <20,000/μL after primary recovery. Of the 40 patients, 4 relapsed within 1 month of SFPR and were therefore regarded as nonfailures for purposes of analysis. Characteristics of patients who achieved primary recovery are reported in Table 1.

Median day of onset of SFPR was day 44 (range, day 24-89) posttransplantation. Of 36 patients, 23 were discharged to home at a median of day 89 (range, day 40-169), and 48% (11 of 23) had recovered to sustained platelet counts with a median duration of SFPR of 10 days (range, 1-92 days). As part of a tandem transplantation protocol, 3 additional patients underwent a second transplantation before leaving FHCRC. The overwhelming majority (95.9%) of patients who did not develop SFPR had follow-up discontinued because they were discharged home. The median duration of the observation period of these patients was 54 days.

Among the 20 patients who developed SFPR and were alive at 1 year, 11 (55%) had platelet counts >50,000/μL, and 5 of 11 were within normal ranges (ie, with platelet counts >150,000/μL). One patient had a platelet count <50,000/μL at 1 year. Data were only available on 6 of these 20 patients, all of whom had platelet counts >50,000/μL, between 4 and 9 months (n = 2) or after 15 months (n = 4). There were 2 patients for whom there were no long-term data on platelet counts.

Concomitant neutropenia was seen in 7 (19%) of 36 patients with SFPR, and 4 of the 7 were on ganciclovir.

Bone marrow aspirates were performed in 13 (36%) of 36 thrombocytopenic patients at a median of 15 days (range, 0-44 days) after the onset of SFPR. Cellularity was read as <35% of normal with no megakaryocytes in 1 of 13 patients as ≥35% of <50% and as ≥50%, with trilineage engraftment in 3 of 13, and 9 of 13 patients, respectively.

Risk Factor Analysis. Univariate models are reported in Table 2. Only CMV infection after primary platelet recovery and source of stem cells were significantly associated with the hazard rate of SFPR. The multivariable regression model containing each of these variables is summarized in Table 3. Addition of age failed to provide a significant improvement in this model (P = .33). Cell dose is highly correlated with source of stem cells, but the addition of cell dose to a model already containing a source of stem cells adds little (P = .60). If one considered the total of primary and secondary failure of platelet recovery combined, there was a 40% and 19% incidence after marrow or peripheral blood stem cell (PBSC) infusion, respectively. Therefore, although there was an increase in the hazard rate of SFPR among those who achieved primary recovery after PBSC infusion, there was a reduction in the overall incidence of failure of platelet recovery.

Platelet Transfusion Requirements. Transfusion requirements for patients undergoing autologous transplantation are reported in Table 4.

Survival. The 1-year mortality of the patients developing SFPR was 44% (16 of 36), and 27% (10 of 36) died before leaving the center. When treated as a time-dependent covariate, SFPR was associated with an increased hazard rate of death (hazard ratio = 2.2; 95% CI, 1.4-3.3; P = .0005) among patients who achieved primary recovery after adjusting for age at transplantation, risk of underlying disease, and preparative regimen. Causes of death are reported in Table 5.

DISCUSSION

SFPR is a significant complication after HSCT that is associated with a poor prognosis. We noted incidences of 20% in allogeneic HSCT recipients and 5% in autologous HSCT recipients. This study likely underestimates the true incidence because patients may develop SFPR after being discharged home, and we were unable to detect such failures. The problems of thrombocytopenia and delayed primary recovery of platelet counts after HSCT have been addressed in several reports [1-5]. However, no previous large study has specifically addressed the issue of thrombocytopenia developing after primary platelet recovery. The analysis of characteristics and risk factors for SFPR are helpful in possibly identifying underlying causes, which are not otherwise clinically evident.

In a recent multicenter study, Bernstein et al. [2] showed that time to primary platelet recovery after allogeneic and autologous HSCT was influenced by baseline clinical and time-dependent variables. These clinical variables were: the number of $CD34^+$ cells infused, pretransplantation platelet count, prior radiation therapy, disease type, type of allogeneic donor, fever, and veno-occlusive disease of the liver. Other

studies have reported enhanced platelet recovery with the use of PBSCs and with greater numbers of $CD34^+$ cells infused [6-8]. Our analysis did not associate source of stem cells among allogeneic recipients or disease type and disease status with a higher risk of development of SFPR, suggesting that SFPR was not influenced by some of the pretransplantation factors that significantly correlate with primary platelet recovery. Source of stem cells was suggestively associated with SFPR among the patients undergoing autologous transplantation, but this was likely related to the fact that more patients were at risk for SFPR after the use of PBSCs. The association of growth factors with SFPR was not included in the analysis because the observed association could have been related to the clinical reasons that growth factors were started.

The only baseline clinical variables significantly associated with SFPR among allogeneic transplantations were transplants from an alternative donor, regimens for GVHD prophylaxis different from the standard combination with CSP and MTX, cell dose infused, and preparative regimen [9]. The effect of CSP and MTX did not appear to be completely explained by the correlation of nonstandard GVHD prophylaxis with risk of underlying disease or by the reduction of the rate of GVHD among patients who received CSP and MTX. Adding GVHD prophylaxis to a regression model that already contained risk of disease and presence of GVHD led to a significant improvement in the model. The majority of patients undergoing allogeneic transplantation received CSP and MTX, and if the analysis was restricted to this group, the overall conclusions were not qualitatively changed (data not shown). The development of acute GVHD (grade 2 to 4) showed a significant association with the hazard rate of SFPR, even after adjusting for other pretransplantation and posttransplantation variables, in particular, variables associated with development of GVHD. Similarly, both the type of GVHD prophylaxis and type of allogeneic donor showed a significant association with the hazard rate of SFPR, even after considering the contribution of GVHD. This result suggested that each of these parameters contributed to the hazard rate of SFPR above and beyond the effect due to GVHD. The development of GVHD had previously been associated with thrombocytopenia [11,12].

In the present report, elevated serum bilirubin levels were used as a surrogate marker for liver dysfunction. Hepatic veno-occlusive disease (VOD) has been associated with persistent thrombocytopenia and refractoriness to platelet transfusions [13,14]. However, the liver dysfunction associated with SFPR was characterized by a median time of onset at day 63, and therefore, many cases were likely related to GVHD or infections rather than VOD [15].

TTP/HUS has been associated with CSP and FK506 toxicities, GVHD, and radiotherapy [16,17]. The incidence, time of onset, and outcome of TTP/HUS vary greatly in HSCT [18-21], and the clinical diagnosis may be difficult [22]. Thrombocytopenia, Coombs-negative hemolytic anemia, renal abnormalities, fever, and altered sensorium [23,24] represent a constellation of features of TTP/HUS that, either isolated or in combination, can be caused by a variety of factors. Red blood cell fragmentation is not specific for TTP/HUS after transplantation because it is also reported in patients without TTP/HUS [16,25,26]. Our study reports clinical evidence of TTP/HUS in only 5% of patients developing SFPR. However, this retrospective analysis may underestimate the true incidence of this problem, and TTP/HUS should always be considered in the differential diagnosis of SFPR.

Systemic fungal and bacterial infections were factors associated with SFPR. Severe thrombocytopenia also occurs in patients with sepsis in the nontransplant setting [27]. It is possible that a common mechanism(s) contributes to the thrombocytopenic states associated with infections or inflammatory diseases [27,28]. One proposed mechanism is a cytokine storm effect, with increased levels of granulocyte colony-stimulating factor, macrophage colony-stimulating factor, and other cytokines, that may activate the monocyte/macrophage system, causing a premature removal of platelets from the circulation (R.A.N., unpublished observations) [29-34].

CMV infections have been shown to be associated with secondary marrow graft failure after allogeneic bone marrow transplantation [35]. In addition, isolated thrombocytopenia has also been observed during CMV infection [36]. Various mechanisms of marrow suppression have been proposed, including direct infection of hematopoietic progenitors, stromal cells or accessory cells leading to cell death, abnormal gene expression, or immune reaction against the infected cells [37-40]. In vitro studies have shown that latent CMV infections can become reactivated during megakaryocytic maturation leading to thrombocytopenia through direct infection [41].

After autologous HSCT, the incidence of SFPR was lower than that after allogeneic HSCT. This is likely related to an increased risk of GVHD and infections after allogeneic HSCT but could also be related to the relative shorter length of follow-up among patients who underwent autologous transplanatation. The relatively low incidence of SFPR after autologous HSCT decreased the statistical power to detect significant predisposing factors among the variables analyzed. There was an apparent increase in the risk of SFPR after autologous HSCT with PBSCs, but a significantly higher proportion of autologous bone marrow recipients had either primary or secondary failure when compared with PBSC recipients. The apparent increased risk of SFPR among those who achieved primary recovery was likely related to the rapid primary recovery of platelet counts after autologous PBSC transplantation and the very low incidence of primary failure of platelet recovery; therefore, factors (ie, CMV) that may have contributed to delayed or failed primary platelet recovery after autologous marrow transplantation caused SFPR instead [1,4].

In summary, SFPR is a significant complication after HSCT. The etiology of SFPR in many cases is likely multifactorial. No events of graft rejection were identified in patients with SFPR. Relapse should always be considered because 13% of patients with SFPR had relapsed within 30 days of onset. The identification of this complication with a description of characteristics and risk factors should improve patient counseling and management. Improved supportive care and prevention of GVHD may reduce the incidence of SFPR. Clinical trials of agents to shorten the duration of thrombocytopenia after transplantation must also consider the incidence, clinical characteristics, and risk factors associated with SFPR in their study design.

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